REMARKS

Reconsideration of the instant application is respectfully requested in view of the amendments above and the following remarks. In response to the Office Action dated December 1, 2008, Applicants amended claims 7, 10, 21, 24, 36 and 39 and added claims 44-49. Based on the foregoing amendments, Applicants contend that the present application is in a condition for allowance.

Applicants invention is directed *inter alia* to methods of inducing bone formation, proteoglycan synthesis, or osteoblast differentiation in a mammal comprising administering an effective amount of a fusion polypeptide comprising a protein transduction domain and an osteoinductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 protein. The osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP, or LMP-1s.

1. Support for Claim Amendments and New Claims.

Applicants amended claims 7, 21, and 36 to recite that the fusion protein comprises a protein transduction domain and at least one polypeptide comprising an isolated osteoinductive region of an LMP-1 protein, wherein the polypeptide has less than 100% sequence homology with LMP-1, or RLMP. Support for this amendment may be found at least in paragraph [43] that states that the peptide may have less than one hundred percent homology or identity to the amino acid sequence of various LIM mineralization proteins.

In addition, Applicants added new claims 43-49 that recite that the fusion polypeptide consists of a protein transduction domain and at least one isolated osteoinductive region of an LMP-1 protein selected from the group consisting of SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8 and combinations thereof. Support for new claims may be found at lest in paragraph 31, which states that the preferred osteoindcutive peptides include regions derived from LMP-1, such as, for example, SEQ ID NO 1, SEQ ID NO 2, SEQ ID NO 3, SEQ ID NO 4, SEQ ID NO 5, SEQ ID NO 6, SEQ ID NO 7, SEQ ID NO 8.

2. Rejections based on 35 U.S.C § 103

Claims 7-9, 12-15, and 36-38 were rejected as being unpatentable under 35 U.S.C. 103(a) as being obvious over Hair et al. (U.S. Patent 6,521,750) or (U.S. 6, 858,431) in view of Nagahara et al.

Claims 7-15, 21-23, 26-30, and 36-38 were further rejected as obvious over Boden (Endocrinology 1998, 139(12): 5125-5134) in view of Nagahara et al. and van Beuningen et al.

Applicants amended claims 7, 21, and 36 to recite that the fusion protein comprises a protein transduction domain and at least one polypeptide comprising isolated osteoinductive region of an LMP-1 protein, wherein the polypeptide has less than 100% sequence homology with LMP-1, RLMP or LMP-1s. In rejecting Applicants' arguments made in the response to the previous office action, the Examiner argued that because claims 7, 21, and 36 use the word "comprising," they include using the full length LMP-1, which is disclosed by Boden et al. or Hair. Applicants further amended claims 7, 21, and 36 to clarify that their methods do not include using polypeptides disclosed in these references.

None of the references cited by the Examiner in her rejection under 35 U.S.C. 103(a) teach or provide for inducing bone formation, proteoglycan synthesis or osteoblast differentiation using a combination of a protein transduction domain and a polypeptide comprising an isolated osteoinductive region of an LMP-1 protein, which has less than 100% sequence homology with LMP-1, RLMP or LMP-1s. Referring first to Boden et al., this publication specifically relates to the first identification of LMP-1 in rats and its function in calvarial osteoblast differentiation, particularly with respect to bone formation. As noted above, Boden does not disclose or suggest inducing bone formation, proteoglycan synthesis or osteoblast differentiation using peptides that comprise an osteoinductive region of LMP-1, but that have less than 100% homology to LMP-1, RLMP or LMP-1s.

Hair et al. (referring to US6521750 or US6858431) is similarly deficient in that there is no discussion or experimentation related to isolating and administering polypeptides comprising an isolated osteoinductive region of LMP-1, that have less than 100% homology with LMP-1, RLMP, or LMP-1s. More particularly, Hair et al. presents the next generation to Boden et al. in that these patents relate to the discovery, isolation, and potential uses of a rat LMP (rLMP) gene, a human LMP (hLMP) gene, and a truncated version of human LMP-1 (hLMP-1s). To this end,

Hair et al. first provides the nucleic acid sequences and amino acid sequences for each of these LMP genes, then further characterizes gene therapy methods of using these sequences so as to facilitate bone formation. However, much like Boden et al., Hair et al. stops short of identifying the specific osteoinductive regions within these proteins. Rather, each of the foregoing nucleic acid sequences and protein sequences of Hair et al. are only contemplated for administration in their entirety and without alterations. As is true with Boden, there is nothing within Hair et al. to teach which region(s) of these genes are actually functional for bone formation or that such regions may be specifically isolated and administered in accordance with the present invention. Accordingly, Hair does not teach or suggest inducing bone formation, proteoglycan synthesis or osteoblast differentiation using peptides that comprise an osteoinductive region of LMP-1, but that have less than 100% homology to LMP-1, RLMP or LMP-1s.

The remaining references cited by the Examiner are not relevant to the isolation and administration of osteoinductive regions of an LMP protein. Specifically, Beuningen et al. relates to local application of BMP-2 for the stimulation of proteglycans, i.e. synthesis of cartilage. There is no discussion within Beuningen et al. relating to the LMP protein. Nagahara et al. also does not teach any aspect of the LMP protein. While the Examiner is correct that Nagahara et al. provides an overview of steps to creating a TAT fusion protein, the specific protein discussed is p27. There is no discussion of any osteogeneic protein, let alone LMP.

Based on the foregoing, there is nothing within the prior art to teach or suggest that any one particular region of the previously known LMP protein is responsible for osteoblast differentiation and/or proteoglycan synthesis. Rather, at best, the references cited by the Examiner teach isolation and characterization of an entire LMP-1, RLMP and LMP-1s protein without alterations. Furthermore, there is nothing in the prior art to provide for the isolation of polypeptides within an osteoinductive region of these proteins such that, upon administration, the polypeptides will provide for osteoinductive functionality, proteoglycan synthesis, or osteoblast differentiation. As noted above, the foregoing claims have been amended to include polypeptides comprising isolated osteoinductive regions of these proteins that have less than 100% homology to LMP-1, RLMP, or LMP-1s. For at least these reasons, Applicants respectfully assert that the present claims, as amended, traverse the Examiner's rejection.

3. Rejections based on 35 U.S.C § 112

Claims 7-15, 21-30 and 36-40 were rejected under 35 U.S.C § 112, first paragraph, as failing to comply with the written description requirement. The Examiner asserts that because the specification does not provide adequate description of the structural and functional relationship of the regions of LMP-1 that comprise osteoinductive activity, it fails to demonstrate that inventors were in possession of the invention at the time the invention was filed. Applicants respectfully disagree.

Applicants respectfully remind the Examiner that MPEP § 2163.04 states that description as filed is presumed to be adequate, unless or until sufficient evidence or reasoning to the contrary has been presented by the examiner to rebut the presumption. See, e.g., *In re Marzocchi*, 439 F.2d 220, 224, 169 USPQ 367, 370 (CCPA 1971). The Examiner, therefore, must have a reasonable basis to challenge the adequacy of the written description. The Examiner has the initial burden of presenting by a preponderance of evidence why a person skilled in the art would not recognize in an applicant's disclosure a description of the invention defined by the claims. *Wertheim*, 541 F.2d at 263, 191 USPQ at 97. Here, the Examiner must provide sufficient evidence that a person of ordinary skill in the art would not recognize in the instant disclosure a description of a genus of osteoiductive polypeptides comprising at least one isolated osteoinductive region of an LMP-1 protein, wherein the osteoinductive polypeptide has less than 100% homology to LMP-1, RLMP, and LMP-1s.

"The fundamental factual inquiry is whether the specification conveys with reasonable clarity to those skilled in the art that, as of the filing date sought, applicant was in possession of the invention as now claimed." MPEP § 2163(I)(B). (Internal citation omitted, emphasis added.) The written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics, i.e., structure or other physical and/or chemical properties, by functional characteristics coupled with a known or disclosed correlation between function and structure, or by a combination of such identifying characteristics, sufficient to show the applicant was in possession of the claimed genus. See MPEP 2163(II)(A)(a). This section states as follows:

> For example, the presence of a restriction enzyme map of a gene may be relevant to a statement that the gene has been isolated. One skilled in the art may be able

> to determine whether the gene disclosed is the same as or different from a gene isolated by another by comparing the restriction enzyme map.

Accordingly, the written description requirement may be met even if a person having ordinary skill in the art is required to perform certain mental steps to determine whether the applicant was in possession of the claimed invention.

Claims 7, 21, 36 were amended to recite that the osteoinductive polypeptide comprises at least a portion of SEQ ID NO: 5. Paragraph 23 of the instant application states as follows:

> Previous work has demonstrated that LIM mineralization protein splice variants 1 and 3 (LMP-1 and LMP-3) are osteoinductive, while LMP-2 does not appear to have such osteoinductive potential. A forty amino acid sequence corresponding to amino acids 94-133 of the amino acid sequence of human LMP-1 (hLMP-1) is common to both LMP-1 and LMP-3. The inventors therefore surmised that this unique region of the proteins might, in itself, have osteoinductive potential. Peptides comprising overlapping segments of this sequence were designed and used to test the inventors' hypothesis

The amino acid sequences for LMP-1, LMP-2, and LMP-3, as well as for rat RLMP and LMP-1s have been disclosed in the prior art. *See e.g.,* U.S. Patent Application Serial Nos. 10/292,951 and 10/382,844. Accordingly, a person having ordinary skill in the art is provided with sufficient guidance to identify the amino acid sequence with the osteoindcutive potential by comparing the amino acid sequences of LMP-1, LMP-2, and LMP-3. In fact, such sequence is represented by SEQ ID NO: 5 in the instant application.

The instant specification also discloses a number of osteoinductive polypeptides comprising overlapping segments of SEQ ID NO: 5, namely peptides represented by SEQ. ID. NOs 1-8, that demonstrated osteoiductive functionality. As shown in Fig. 6, introducing these peptides into cells as part of the fusion protein induces bone growth. However, as Fig. 6 shows, peptides represented by SEQ. ID. NOs 1-8 have varying degree of osteoinductive activity. For example, introducing into a cell 25 nM of Peptide of SEQ ID NO: 3 results merely in some bone growth, whereas lesser amount of Peptides of SEQ ID NO: 2, SEQ ID NO: 4, and SEQ ID NO: 7 cause higher level of bone growth. Furthermore, although peptides SEQ ID NOs 1, 5, 6, and 8 resulted in similar degree of bone growth as the peptide of SEQ ID. NO 3, much smaller amounts of these peptides were used. Comparing the structure of Peptide of SEQ ID NO: 3 with

the structure of other peptides reveals that the same amino acid sequence is present in all peptides, except Peptide of SEQ ID NO: 3. A person having ordinary skill in the art would have been able to identify this sequence as Gly Ala Pro Pro Pro Ala Asp Ser Ala (GAPPPADSA), and recognize its functional importance. *See* Exhibit A.

Accordingly, one having ordinary skill in the art would recognize that Applicants were in possession of the claimed genus as Applicants have disclosed a sufficient number of species of the osteoinductive polypeptide comprising at least one isolated osteoinductive region of an LMP-1 genus in combination with description of the structure of the species that is responsible for the osteoinductive functionality of these species. "[T]here is no per se rule that an adequate written description of an invention that involves a biological macromolecule must contain a recitation of known structure." *Falkner v. Inglis*, 79 SUPQ2d 1001, 1007 (Fed. Cir. 2006).

Applicants further submit that the instant specification provides sufficient evidence that the representative species recited therein can induce proteoglycan synthesis or osteoblast differentiation. According to MPEP § 2163(II)(A)(3)(b), when a claim limitation is not explicitly described in the specification, the written description may be met by showing that such limitation is supported in the original disclosure implicitly or inherently. Applicants respectfully submit that a person with ordinary skill in the art would have understood from the instant disclosure that administering of the claimed peptides to a cell would induce proteoglycan synthesis and osteoblast differentiation.

As noted above, Fig. 6. shows that peptides disclosed in the instant specification induce bone growth. A person having ordinary skill in the art would have reasonably inferred that the osteogenic effect of these peptides is likely due, at least in part, to these peptides' ability to induce BMP synthesis because BMP's is known to play an important role in bone formation and growth. It is also well know that BMP increases proteoglycan production as well as induces osteoblast differentiation. *See e.g.,* U.S. Patent Application Serial Nos. 10/292,951. Therefore, the person of ordinary skill in the art would have concluded that the peptides that induce bone formation (e.g., peptides with osteoiductive functionality) would also induce proteoglycan synthesis and osteoblast differentiation.

In light of the foregoing, Applicants respectfully request that the Examiner withdraw this ground for rejection. Applicants note that if the Examiner does not find Applicants' arguments persuasive, she should provide scientific reasoning of his conclusion. Applicants note that "[a]

general allegation of "unpredictability in the art" is not a sufficient reason to support a rejection for lack of adequate written description." MPEP § 2163.04.

D. Double Patenting Rejections.

Applicants also assert that the presently amended claims overcome the Examiner's double patenting rejections over claims 1-13 of U.S. Patent No. 6858431 ("the '431 patent"), in view of a combination of Nagahara et al.

As set forth above, the '431 patent contemplates administering LMP-1, RLMP, and LMP-1s in their entirety without alterations. It does not teach or suggest administering a polypeptide comprising of an osteoinductive region within these proteins but having less than 100% homology to these proteins. Nagahara et al. does not account for this deficiency. Rather, Nagahara et al. only provides an overview of steps to creating a TAT fusion protein. There is no discussion of any osteogeneic protein, let alone LMP. Accordingly, the '431 patent and Nagahara et al. in combination do not render the present claims as obvious.

In light of the foregoing, Applicants respectfully assert that the present claims, as amended, traverse the Examiners rejection, and Applicants respectfully request that the Examiner withdraw her nonstatutory obviousness-type double patenting rejection and allow these amended claims.

CONCLUSION

Applicants believe that they have fully responded to the Examiner's concerns, and the claims of the instant application are in condition for allowance. Applicants request that any questions concerning this matter be directed to the undersigned at (901) 399-2652.

Please charge any deficiency and/or credit any overpayment to Deposit Account No. 132546. Thank you for your kind consideration in this matter.

Respectfully submitted,

Samir R. Patel
Registration No.: 44,998
Attorney for Applicants

Medtronic
Spinal and Biologics
2600 Sofamor Danek Drive
Memphis, TN 38132
Telephone No.: (901) 399-2652

EXHIBIT A:

SEQ ID 1: APSVSLNKTARPF**GAPPPADSA**

SEQ ID 2: ARPF**GAPPPADSA**PQQNGQPLR

SEQ ID 3: KPQKASAPAADPPRYTFAPSVS

SEQ ID 4: LNKTARPF**GAPPPADSA**PQQNG

SEQ ID 5: ASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG

SEQ ID 6: SKPQKASAPAADPPRYTFAPSVSLNKTARPF**GAPPPADSA**PQQNG

SEQ ID 7: **GAPPPADSA**PQQNGQPLRPLVPDASKQRLM

SEQ ID 8: **GAPPPADSA**PQQNGCRPLTNSRSDRWSQMP